--84. (New) The immunogen according to claim 52 wherein said HCV amino acid sequence is immunogenic.--

--85. (New) A composition comprising an immunogen according to any one of claims 40 to 47, or 52 to 59 and a pharmaceutically acceptable excipient.--

--86. (New) A composition comprising an immunogen according to claim 64 and a pharmaceutically acceptable excipient.--

--87. (New) A composition comprising an immunogen according to claim 69 and a pharmaceutically acceptable excipient.--

REMARKS

Claims 1 to 39 have been canceled. Claims 40 to 87 are pending. With respect to claims 1 to 39, Applicants do not concede that these claims are not patentable and reserve the right to pursue the same or similar subject matter in a continuing application or other related application. Applicants submit that the amendments to the claims are made solely to clarify that which applicants regard as their invention and not to overcome the cited prior art. Cancellation of claims 1-39 does not constitute an admission that these claims were not enabled. Applicants expressly reserve their right under 35 U.S.C. § 121 to file divisional applications directed to the non-elected subject matter during the pendency of this application.

Regarding Amendments to the Claims:

The amendments to the claims are to clarify the nature of the subject matter claimed. Support for the claims is found throughout the specification, therefore, the amended claims do not constitute new subject matter. Specifically, support can be found for the claims, for example, in the following pages and lines of the present specification: Section II.C. Preparation of

Antigenic Polypeptides and Conjugation with Carrier - page 47, line 24 through page 53, line 36; Section II.D. Preparation of Hybrid Particle Immunogens Containing HCV Epitopes - page 54, line 1 through page 55, line 3; Section II.E. Preparation of Vaccines - page 55, line 5 through page 58, line 29; Section II.F. Dosage and Administration of Vaccines - page 58, line 31 through page 59, line 21; Section II.G. Preparation of Antibodies Against HCV Epitopes - page 59, line 23 through page 61, line 2.

As indicated on page 255, lines 12-21 the American Type Culture Collection samples listed in the claims were deposited on the following dates: ATCC No. 40394 was deposited on December 1, 1987; ATCC No. 40388 was deposited on November 17, 1987; ATCC No. 40389 was deposited on November 17, 1987; ATCC No. 40390 was deposited on November 17, 1987; ATCC No. 40391 was deposited on November 18, 1987; ATCC No. 40514 was deposited on November 10, 1988; ATCC No. 40511 was deposited on November 10, 1988; ATCC NO. 40512 was deposited on November 10, 1988; and ATCC No. 40513 was deposited on November 10, 1988.

35 U.S.C. § 112, 2nd Paragraph Rejections:

Claims 20, 38, and 39 have been rejected under 35 U.S.C. § 112, second paragraph as indefinite with respect to the amino acid sequences to be used in the present invention, and the use of the terms: "immunogenic against," "HCV epitope," "isolated," "immunogenic polypeptide," and "administering in an amount sufficient to produce an immune response." Applicants respectfully traverse these rejections as well as the supporting remarks.

The Federal Circuit has held that "[t]he legal standard for definiteness is whether a claim reasonably apprises those of skill in the art of its scope." *In re Warmerdam*, 33 F.3d 1354 (Fed.Cir. 1994); also see *Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.*, 927 F.2d 1200 (Fed. Cir. 1991). In making a § 112, second paragraph rejection, "[t]he PTO ha[s] the initial burden of presenting evidence or reasons why a person skilled in the art would not recognize in the

disclosure a description of the invention defined in the claims." *In re Gosteli,* 872 F.2d 1008 (Fed. Cir. 1989).

Amino Acid Sequences to be Used:

The HCV amino acid sequences used in the compositions of the invention are described throughout the present application. The claims recite the term "immunogenic." Guidance in determining which HCV sequences are for use in the compositions of the invention, is also provided, for example, in Section II.C. Preparation of Antigenic Polypeptides and Conjugation with Carrier, page 47, line 24 through page 53, line 36; and the amino acid sequences disclosed in, *inter alia,* Figures 14, 47, 66, and 90. In addition please note that all of the pending claims require the use of a polypeptide comprising an "amino acid sequence of at least 8 contiguous amino acids encoded by the genome of a hepatitis C virus." This language in combination with the description and characterization of HCV and the HCV amino acid sequences disclosed throughout the present application provide an exacting definition of which HCV sequences fall within the scope of the pending claims. Applicants submit that a broad claim, no matter how broad, is not indefinite as long as the boundaries of the claim are capable of being understood. See, e.g., MPEP § 706.03(d): "[i]f the scope of the claimed subject matter can be determined by one having ordinary skill in the art, a rejection ... [under 35 U.S.C. § 112, second paragraph] is not appropriate."

The specification likewise provides additional guidance as to the use of particle forming polypeptide sequences. See, e.g., Section II.D. Preparation of Hybrid Particle Immunogens Containing HCV Epitopes, page 54, line 1 through page 55, line 3, which describes Hepatitis B surface antigens and Hepatitis B presurface regions. As is iterated in the Office Action for the rejection under 35 U.S.C. § 103(a), particle forming sequences and their immunogenic properties were well known in the art at the time the earliest priority document was filed. See, e.g., Valenzuela *et al.* US. Patent No. 5,089,704; 1982 Nature 298:347; and 1985 Bio/technology 3:323. Specifically the Bio/technology article demonstrates that methods for determining the immunogenicity of a chimeric particle can be readily determined by empirical methods known in

the art. Since the language of the claims is clear and the immunogenicity of the particle can be determined, the scope of these claims is well defined.

Immunogenic Against:

Applicants submit that the term "immunogenic against" is a term of art with a meaning that is understood by practitioners in this field. In its definition of the term "immunogenic polypeptide" on page 35 lines 1-4, the present application states that a particle that is "immunogenic against" HCV infection would elicit a cellular and/or humoral immune response. While such a response might provide protective and/or therapeutic immunity, the particle would not be required to do so under this definition. Nevertheless, none of the pending claims includes the term "immunogenic against."

HCV Epitope:

Applicants submit that the term "epitope" was widely known and used at the time the earliest priority document was filed. With all of the information provided by the present application relating to identifying and characterizing HCV, the meaning of "HCV epitope" is abundantly clear. In addition, the term "epitope" is specifically defined for use in the present application. See page 31, lines 13 to 21. Moreover, methods of locating epitopes are described throughout the present application, including for example page 50, lines 10 to 32. Nevertheless, to expedite prosecution the term "epitope" has been removed from the claims.

Isolated:

Applicants submit that the term "isolated" as applied to polypeptides was widely known and used at the time the earliest priority document was filed. Moreover, the term "isolated" is defined in the present application, and is often used interchangeably with the term "purified" in this art to refer to polypeptide preparations having a concentration that is higher than occurs naturally. In the present application the definition of "purified viral proteins" is presented on page 29, lines 17 to 24. Methods of purifying or isolating polypeptides are described throughout the present application, including, for example, page 47, lines 5-12. Nevertheless, to expedite prosecution the term "isolated" has been removed from the claims.

Immunogenic Polypeptide:

The term "immunogenic polypeptide" widely known and used at the time the earliest priority document was filed. Moreover, the present application provides a precise and succinct definition for the term "immunogenic polypeptide" on page 35, lines 1 to 4. An immunogenic polypeptide "is a polypeptide that elicits a cellular and/or humoral immune response, whether alone or linked to a carrier in the presence or absence of an adjuvant." Thus, the immunogenic polypeptides of the invention would elicit the production of antibodies, a cellular immune response, or both. A prophylactic or therapeutic immunity might often result from the administration of these immunogenic polypeptides, but the definition does not require any such immunity of an immunogenic polypeptide. Determining whether a candidate polypeptide elicits the production of antibodies, a cellular immune response, or both is within the skill of one in the art. Thus, the requirement under *In re Gosteli* to sustain a § 112, second paragraph rejection has not been met, since the record contains no evidence or reason why a person skilled in the art would not recognize in the disclosure a description of the invention defined in the claims.

Administering in an Amount Sufficient to Produce an Immune Response:

According to the Office Action "administering in an amount sufficient to produce an immune response" required clarification as to the particular amounts and schedules, as well as the metes and bounds of an immune response. Applicants submit that the approximate amounts of an immunogen used and the approximate immunization schedules are widely known in the art, while the specific amounts and schedules are easily and routinely determined by empirical means. In addition, the present specification provides thorough guidance for determining the appropriate dosage amount and immunization schedule to be used. See, for example, Section II.F. Dosage and Administration of Vaccines, page 58, line 31 through page 59, line 21, as well as Section II.G. Preparation of Antibodies Against HCV Epitopes, page 59, line 23 through page 61, line 2.

An immune response may be humoral (antibody-based) or cellular in nature, and need not result in a protective or therapeutic immunity. The pending claims and the definition section of the specification are not consistent with a requirement that the term "immune response" have a protective effect. In order to expedite prosecution, the pending claims have been drafted to point

out that for the methods for producing antibodies, the immunogen is administered in a sufficient amount to elicit a humoral immune response. Since the record contains no evidence or reason why a person skilled in the art would not recognize in the disclosure a description of the invention defined in the claims, the requirement under *In re Gosteli* to sustain a § 112, second paragraph rejection has not been met.

For all of the above-stated reasons, Applicants submit that the claims are definite and meet all of the legal requirements under 35 U.S.C. § 112, second paragraph. Thus, Applicants respectfully request that the 35 U.S.C. § 112, second paragraph rejections directed to the amino acid sequences to be used in the present invention, and the use of the terms: "immunogenic against," "HCV epitope," "isolated," "immunogenic polypeptide," and "administering in an amount sufficient to produce an immune response" be reconsidered and withdrawn.

35 U.S.C. § 112, 1st Paragraph Rejection (Protective Immunity):

Claim 32 has been rejected under 35 U.S.C. § 112, first paragraph as nonenabling for the production of protective immunity to HCV. Applicants respectfully traverse this rejection as well as the supporting remarks.

35 U.S.C. § 112, first paragraph requires a patent to contain a description that enables one skilled in the art to make and use the claimed invention. *Atlas Powder Co. v. E. I. du Pont de Nemours & Co., 750 F.2d 1569, 1576 (Fed. Cir. 1984).* The present specification thoroughly describes how to make and use compositions which do produce protective immunity. See, for example, Section II.E. Preparation of Vaccines - page 55, line 5 through page 58, line 29; and Section II.F. Dosage and Administration of Vaccines, page 58, line 31 through page 59, line 21.

The rejection appears to be based on the contention that the lack of protective immunity is the host's inability to generate HCV neutralizing antibodies. However, the pending vaccine composition claims (claims 74-78) do not require these compositions to elicit protective immunity or stimulate the generation of HCV neutralizing antibodies. The pending vaccine composition claims all depend from claims 40 or 52, either directly or indirectly, and thus are required to "elicit an anti-HCV immune response when administered to a mammal." Moreover, the specification does not teach that the vaccines must produce neutralizing antibodies.

Nevertheless, Applicants have demonstrated a strong humoral immune response and protection of chimpanzees against experimental challenge with HCV using a vaccine comprising recombinant gpE1 and gpE2 envelope proteins. See Choo *et al.* Proc. Nat'l. Acad. Sci. USA-1994 91:1294-1298 (attached). Thus, Applicants submit that vaccine compositions which elicit protective immunity are enabled by the present specification, but that none of the pending claims including those directed to vaccine composition require that protective immunity result.

This rejection also appears to be based, in part, upon an alleged lack of utility. See the outstanding Office Action which states "none of the potential HCV vaccines had been successful in the induction of protective immunity." Applicants submit that they have already met the burden for demonstrating utility under 35 U.S.C. § 101 and enablement under 35 U.S.C. § 112 for the vaccines of the present application. As noted above, the Choo *et al.* reference discloses a vaccine of the present invention successfully used to induce protective immunity in chimpanzees. The Federal Circuit has held that *in vivo* demonstrations of efficacy in animal models are sufficient to prove pharmaceutical utility of an invention. *In re Brana*, 51 F.3d 1560, 1566-8 (Fed. Cir. 1995); also see *In re Krimmel,* 292 F.2d 948, 953 (CCPA 1961). In addition see *Scott v. Finney*, 34 F.3d 1058, 1063 (Fed. Cir. 1994) ("Testing for the full safety and effectiveness of a prosthetic device is more properly left to the Food and Drug Administration (FDA). Title 35 does not demand that such human testing occur within the confines of Patent and Trademark Office (PTO) proceedings.")

Therefore, the specification enables the production and use of vaccines which provide protective immunity. Applicants submit that the claims and specification meet the requirements under 35 U.S.C. § 112, first paragraph and request that the rejection be withdrawn.

35 U.S.C. § 112, 1st Paragraph Rejection (Immunogenic Polypeptides and HCV Epitopes):

Claims 20, 32, 38 and 39 have been rejected under 35 U.S.C. § 112, first paragraph as allegedly nonenabling for the location and identification of "immunogenic polypeptides" and "HCV epitopes." Applicants respectfully traverse this rejection and its supporting remarks.

To be enabling under §112, a patent must contain a description that enables one skilled in the art to make and use the claimed invention. *Atlas Powder Co. v. E. I. du Pont de Nemours &*

Co., 750 F.2d 1569, 1576 (Fed. Cir. 1984). That some experimentation is necessary does not constitute a lack of enablement; the amount of experimentation, however must not be unduly extensive. *Id*

The pending claims are now directed to HCV immunogens comprising immunogenic polypeptides and methods of their use wherein the immunogenic polypeptides comprise an "amino acid sequence of at least 8 contiguous amino acids encoded by the genome of a hepatitis C virus." Any HCV amino acid sequence disclosed in the present invention can be readily screened to determine if it is immunogenic. Prospective polypeptide sequences need only be prepared and injected into a mammal with the appropriate carriers and/or adjuvants as described in Section II.C. Preparation of Antigenic Polypeptides and Conjugation with Carrier - page 47, line 24 through page 53, line 36; and Section II.G. Preparation of Antibodies Against HCV Epitopes - page 59, line 23 through page 61, line 2. Guidance as to which protein domains within HCV are likely to contain immunogenic polypeptides useful in the preparation of vaccines is provided, for example, from page 55, line 5 through page 56, line 25. If the mammal's serum will contain antibodies which specifically bind to HCV antigens, then one of ordinary skill in the art would determine that the candidate polypeptide sequence was indeed immunogenic. This type of screening was routinely practiced at the time the earliest priority document was filed.

The statements in the Office Action appear to reject Applicants' broad genus claim for an alleged lack of enablement of distinct subgenera or species. The essential question, however, is whether the enablement of the claims is as broad as the scope of the claims. *Amgen, Inc. v. Chugai Pharmaceuticals Co., Inc. and Genetic Institute, Inc., 927 F.2d 1200, 1212 (Fed. Cir. 1991).* Thus, in order to make a prima facie enablement rejection, the Examiner must first show that the artisan of ordinary skill, when provided with the specification, could not have practiced the claimed invention without undue experimentation. *Atlas Powder Co.* at 750 F.2d 1576. Applicants submit that, for the reasons enumerated herein, the claims are enabled across the breadth of their scope.

In addition, the law does not require the mapping of all immunogenic polypeptides, nor the best of them, for that is not what is claimed. Applicants are under no obligation to disclose every immunogenic polypeptide that will work. Cf. *In re Angstadt and Griffin*, 190 USPQ 214

(CCPA 1976).[1] Applicants submit that under the guidelines of *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) sufficient teaching has been provided in the application to allow one of ordinary skill in the art to make and use the claimed immunogens and to practice the claimed methods of preparing antibodies.

In *Wands* the issue was whether immunoassay claims were enabled under 35 U.S.C. § 112, first paragraph. The broadest method claim read:

> 1. An immunoassay method utilizing an antibody to assay for a substance comprising hepatitis B-surface antigen (HBsAg) determinants which comprises the steps of:
> contacting a test sample containing said substance comprising HBsAg determinants with said antibody; and
> determining the presence of said substance in said sample;
> wherein said antibody is a monoclonal high affinity IgM antibody having a binding affinity constant for said HBsAg determinants of at least 10^9 M^{-1}. (*Wands* at 1402).

The position of the PTO was that the production of high-affinity IgM anti-HBsAg antibodies is unpredictable and unreliable, so that it would require undue experimentation for one skilled in the art to make the antibodies. The Court, however, concluded that based upon the facts it would not require undue experimentation to obtain antibodies needed to practice the invention, and the rejection of the claims for lack of enablement under U.S.C. § 112 was reversed.

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[1] The claimed invention was to a method of catalytically oxidizing secondary or tertiary alkylaromatic hydrocarbons to form a reaction mixture comprising the corresponding hydroperoxide. The method employed an organometallic complex as the catalyst. It had been found that Appellants had not disclosed every catalyst that would work in the reaction. In fact, the Appellants had disclosed 40 catalysts out of "thousands" that could possibly work. The Court, in finding that the specification was enabling said:

> "The question, then, is whether in an unpredictable art, section 112 requires disclosure of a test with *every* species covered by a claim. To require such a complete disclosure would apparently necessitate a patent application or applications with "thousands" of examples or the disclosure of "thousands" of catalysts along with information as to whether each exhibits catalytic behavior resulting in the production of hydroperoxides. More importantly, such a requirement would force an inventor seeking adequate patent protection to carry out a prohibitive number of actual experiments. This would tend to discourage inventors from filing patent applications in an unpredictable area since the patent claims would have to be limited to those embodiments which are expressly disclosed. A potential infringer could readily avoid "literal" infringement of such claims by merely finding another analogous catalyst complex which could be used in "forming hydroperoxides." *In re Angstadt,* p. 218.

The Court in *Wands* stated that enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. According to the Court, "the key word is 'undue,' not experimentation." *Wands* at 1404 (emphasis added). The Court, quoting *In re Jackson* (217 USPQ 804, at 807 (Bd. App. 1982)), further stated,

> The determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art (citations omitted). The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. (*Wands* at 1404).

The facts in *Wands* that allowed a finding of enablement were the following. The monoclonal antibodies needed to perform the immunoassays could be made from readily available starting materials using methods that were well known in the monoclonal antibody art, as in the present case. The application of the known methods to make high-affinity IgM anti-HBsAg antibodies required two screening steps, both of which were routine, and a commercial kit was available for one of these steps. Six out of 10 fusion experiments yielded hybridomas that made antibodies specific for HBsAg.

In their analysis, the Court stated that when Wands' data are interpreted in a reasonable manner, analysis considering the factors enumerated in *Ex Parte Forman* leads to the conclusion that undue experimentation would not be required to practice the invention. Wands' disclosure provided direction on how to practice the claimed invention and presented working examples. There was a high level of skill in the art at the time the application was filed, and all of the methods needed to practice the invention were well known. Wands carried out the entire procedure for making the antibodies three times, and was successful each time in making at least one antibody that satisfied all of the claim limitations.

Similar to the situation in *Wands*, Applicants' disclosure provides considerable direction and guidance on how to practice the claimed invention. It is undisputed that the level of skill in the relevant art is very high, and is, in fact, a field of art that overlaps significantly with the field at issue in *Wands*. The specification, as well as the Examples, are replete with teachings of how to prepare candidate polypeptides for use in the claimed immunogens and methods, as well as

methods of screening the candidate polypeptides for immunogenicity. In the present application working examples of immunogenic polypeptides are disclosed in Example IV.B.8.a. Polypeptides Expressed in E. coli, page 147, line 7 through page 153, line 4 (particularly the table of proven immunogenic polypeptides listed on page 152). Moreover, Choo *et al.* Proc. Nat'l. Acad. Sci. USA-1994 91:1294-1298 (attached) demonstrates an immunogen which gives rise to "strong humoral immune response" when administered according to the methods of the present invention or when used as an immunogen of the present invention. Thus, the pending claims meet all of the requirements of the enablement test enunciated in *Wands*.

Should the Examiner chose to maintain this rejection Applicants request that the Examiner provide evidence supporting this rejection pursuant to 37 C.F.R. §1.107(b).

The pending claims may be practiced throughout the entirety of their scope without undue experimentation, the legal standard stated in *Atlas Powder v. DuPont*, and *In re Wands.* Therefore, the claims meet the requirements for enablement under 35 USC § 112, first paragraph. Accordingly Applicants request that the rejection under 35 U.S.C. § 112, first paragraph be withdrawn.

35 U.S.C. § 102 Rejections:

Claims 32, 38, 39 were rejected under 35 U.S.C. § 102(b) as anticipated by Wands (U.S. Patent Nos. 4,271,145 and 4,491,632), Tabor (U.S. Patent Nos. 4,395,395 and 4,356,164) and Coursaget (U.S. Patent No. 4,464,747). Similarly, claims 32, 38, 39 were rejected under 35 U.S.C. § 102(e) as anticipated by Seto *et al.* (U.S. Patent Nos. 4,673,634), Wands (U.S. Patent Nos. 4,870,026), and Pillot (U.S. Patent No. 4,871,659). None of these references, however, reports the successful production of HCV particles, or vaccines, or successful methods of making antibodies to HCV.

Wands - U.S. Patent Nos. 4,271,145 and 4,491,632:

Both U.S. Patent Nos. 4,271,145 and 4,491,632 to Wands allegedly disclose methods of producing antibodies to antigens from Hepatitis A, B, and non-A, non-B viruses; however, the only antigens that Wands even claims to have or be able to isolate are hepatitis B surface

antigens. At no point in these patents does Wands claim to be in possession of a non-A, non-B antigen, nor does he purport to be able to isolate one. These patents do not describe or even suggest a method for producing antibodies to any non-A, non-B hepatitis virus, and most certainly do not claim to disclose the production of antibodies to hepatitis C viral antigens. Hepatitis C antigens were not available until Applicants isolated them for the first time. Any suggestion by Wands to make antibodies from non-A, non-B hepatitis was of no use to an artisan in this field. Without the HCV antigens no antibody could be made. Thus, Applicants respectfully request that the 35 U.S.C. § 102(b) rejection be withdrawn.

Tabor - U.S. Patent Nos. 4,395,395 and 4,356,164:

Both U.S. Patent Nos. 4,395,395 and 4,356,164 to Tabor disclose an antigen allegedly associated with NANBH. The antigen was reportedly detected by counterelectrophoresis in serum samples from chimpanzees during the acute phase of experimentally induced NANBH, using antiserum from a chimpanzee convalescent from human NANBH. According to Seto et al., however, Tabor's antigen-antibody tests for non-A, non-B hepatitis suffer "the disadvantages of non-specificity, insensitivity, and most importantly, the uncertainty of viral or host origin of the antigens and antibodies." (U.S. Patent No. 4,673,634, col. 1, lines 31-36) Thus, there is no definitive evidence that Tabor identified any hepatitis antigen, let alone an HCV antigen. Tabor never claims that the antigen that he observed was of viral origin. Tabor's antigen may very well have been a host antigen which was associated with one or more non-A, non-B hepatitis viruses, like those described by Shimizu *et al. Proc Nat'l Acad Sci USA* (1985) 82:2138–2142; and Shimizu *et al.* 1986 *Hepatology* 6(6): 1329-1333. The Shimizu antibodies were originally thought to be to a NANB antigen but were later discovered to be against a host encoded protein. Moreover, there is no definitive evidence that HCV was the virus which infected the human or chimpanzee subjects of Tabor's study. Thus, Applicants request that the 35 U.S.C. § 102(b) rejection be withdrawn.

Coursaget - U.S. Patent No. 4,464,747 ('747 patent):

The '474 patent describes a particle purportedly found in body fluids from NANB hepatitis patients. It is stated that the particle resembles a togavirus, ranges from 50 to 60 nm in diameter and has a core particle size of about 40 nm. This particle is apparently also described in Coursaget et al., Lancet 2:92, 1979. The following comments demonstrate the non-identity of the Coursaget particle with HCV.

First, Coursaget's work has not been accepted as having identified the etiologic agent of parenterally transmitted NANB hepatitis (pt-NANBH). U.S. Patent No. 4,702,909 issued to Villarejos et al. (the '909 patent), claiming priority from applications filed in 1984 and in 1982, dismissed the Coursaget particle as the etiologic agent of parenterally transmitted NANBH. Villarejos stated:

> In 1979 Coursaget et al., described 60 nm particles resembling toga-virus found in urine and some times in serum of non-A, non-B hepatitis. None of these particles have been shown to be consistently associated with the illness; therefore, it has been concluded that the specific agent of non-A, non-B hepatitis has not yet been discovered.... This subject has been reviewed by R. J. Gerety (Non-A, Non-B Hepatitis, Academic Press, 1981, Chapter 13, pp 207-228), who concludes that neither viral particles nor antigens specific for non-A, non-B hepatitis have yet been positively identified. In summary, it is apparent that no specific relationship to non-A, non-B hepatitis infection can be claimed for the diverse particles and antigens found up until now. [Column 2, lines 8 to 14, 45 to 53.]

In addition, Dienstag, in a 1983 review article reported on a number of virus-like particles described in materials from patients and experimental animals with NANBH and implicated donors or blood products. Included in these particles were those described by Coursaget in the Lancet article. Dienstag stated the following conclusion concerning the reported particles.

> [D]espite a plethora of reports to the contrary, no viral agent or immunologic marker has been identified that fulfills accepted serologic criteria for a specific association with NANB hepatitis.... No serologic relationship between these particles and NANB hepatitis, however, has been demonstrated, and the multiplicity of virus types and sizes observed underscores the caution with which these reports must be interpreted. Those who have extensive experience with electron microscopy of human tissues and fluids are well aware of the ubiquity of visual artifacts and virus-like particles in these materials. [Dienstag, Gastroenterology (1983) 85:743-68, at pp. 748 and 751].

Thus, it is clear that the workers in the NANBH field considered the work reported in the '474 patent to be a false lead.

Second, the inventors themselves commented in the '474 patent that, unexpectedly, the particle was found in urine with more consistency than in serum. It was not found in serum from acute NANBH patients, and was found in serum from only one of eight hemodialysis patients with elevated serum glutamate-pyruvate transaminase activity. [Column 2, line 52 to column 3, line 10]. However, using a PCR assay for the presence of the viral RNA, it has been reported that HCV is always detectable in acute phase serum of HCV infected chimpanzees. Viral RNA is indicative of the presence of virus. Farci, *et al.*, J. Infectious Diseases (1992) 165:1006-1011. It has also been reported that 81% of patients with chronic liver disease and positive by immunoassay for anti-HCV antibodies were positive for HCV RNA in serum. Of those patients that were positive for HCV RNA in the serum, only 7% were positive for HCV RNA in urine. Liou *et al.*, J. Med. Virol. (1992) 37:197-202. Thus, HCV is present in all or the majority of acute phase and chronic phase sera and only a minority of urine samples; the abundance of Coursaget's antigen is the opposite.

Finally, the '474 patent reports a core particle size of about 40 nm in diameter. In contrast, Takahashi et al., report a size of 33 nm for HCV core particles. (The 33 nm particles were reportedly identified as bona fide HCV particles by immunoassay, as well as by identification of HCV RNA.) Takahashi et al., Virology 191:431-434 (1992). Measurement of particle size by electron microscopy is usually fairly precise, typically to $\pm$ 1 nm. For example, the particle sizes of other hepatitis agents have all been determined to two significant figures; i.e., HAV particles are 27 nm, HDV particles are 36 nm, Dane particles (HBV) are 40 nm, and hepatitis B surface antigen particles (HBsAg) are 26 nm. Thus, the difference in size between the Coursaget core particle (40 nm) and the reported HCV core particle (33 nm) is significant.

Thus, the particle described by Coursaget in the '474 patent is not the etiologic agent of HCV infection discovered by Applicants. Thus, the Examiner is respectfully requested to reconsider and withdraw this rejection under 35 U.S.C. § 102(b) over the '474 patent.

Wands (U.S. Patent Nos. 4,870,026)

First, it appears that there has been a minor typographical error. U.S. patent No. 4,870,016 was granted to Levesque *et al.* for a method of making enzymes soluble in organic solvents. Applicants believe that U.S. patent No. 4,870,026 to Wands was meant to cited.

However, this patent to Wands discloses a DNA virus which hybridizes with hepatitis B virus (HBV) DNA. HCV is not a DNA virus and does not have sufficient sequence homology with HBV to hybridize to any significant extent. The virus disclosed by Wands in the 4,870,026 patent could not be HCV. Thus, the Examiner is respectfully requested to reconsider and withdraw these rejections under 35 U.S.C. § 102(b) and § 102(e).

Seto *et al.* (U.S. Patent Nos. 4,673,634)

U.S. Patent Nos. 4,673,634 to Seto discloses a putative NANB associated antigen, which is reportedly present on the surface of virus particles "at a density of 1.14 g/ml". The claims are directed towards the isolated antigen, antibodies specifically reactive to the antigen, a pharmaceutical composition comprised of an immunogenic amount of the antigen, and a kit for screening or detecting a carrier of NANBH, comprised of the purified antigen. Moreover, Seto published an earlier article demonstrating that her 1.14 g/ml antigen had reverse transcription activity (Seto, et al., "Detection of Reverse Transcriptase Activity in Association with the Non-A, Non-B Hepatitis Agent(s)," The Lancet, Saturday October 27, 1984, pp. 941-943). HCV is not a retrovirus, therefore, it is not associated with reverse transcriptase activity. Thus, the Seto virus was not HCV, and the Examiner is respectfully requested to reconsider and withdraw this rejection under 35 U.S.C. § 102(e).

Pillot - U.S. Patent No. 4,871,659:

U.S. Patent No. 4,871,659 to Pillot discloses an anti-NANBH antibody, and processes relating thereto, comprising IgM isolated from sera of monkeys artificially infected with extracts of feces from NANBH patients. The hepatitis C virus is known to be transmitted by blood transfusion and not through fecal material. Thus, the disease agent examined by Pillot was not HCV. In fact in column 6 lines 58 through 64, Pillot explains that the hepatitis virus which he has isolated is different from hepatitis A and hepatitis B, as well as being "different from the two types of NANB hepatitis transmitted by blood transfusions." Thus, Pillot demonstrates that he

has not discovered HCV, and any antibodies which he has produced are not directed to HCV antigens.

None of the cited references report successful production of antibodies to HCV, nor even the successful isolation of HCV antigens. Applicants therefore request that the rejections under 35 U.S.C. § 102(e) be reconsidered and withdrawn.

35 U.S.C. § 103 Rejections:

Claim 20 was rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Valenzuela (US. Patent No. 5,089,704; 1982 Nature 298:347; and 1985 Bio/technology 3:323) in view of Seto *et al.* (U.S. Patent No. 4,673,634). As discussed above, the agent described by Seto *et al.* in U.S. Patent 4,673,634 is a retrovirus and is thus not HCV. HCV antigens and polynucleotide sequences were not available until the present inventors first isolated, sequenced and characterized HCV. The method described by Valenzuela in 1985 Bio/technology 3:323 relies on a scientist's ability to produce a vector which expresses a chimeric protein consisting of both HBsAg and another antigen such as a herpes antigen. Even assuming *arguendo* that Seto *et al.* had isolated an HCV antigen which they had not, Seto did not disclose any nucleotide sequence encoding the antigen. Without this sequence data, it would be impossible to produce a vector encoding the chimeric protein. This sequence information was not available for the Seto antigen, nor was it available for actual HCV antigens prior to the filing date of the earliest filed priority document in the present case. Thus, the method disclosed in Valenzuela in 1985 Bio/technology 3:323 would not have been applicable to HCV without a knowledge of the sequence.

Moreover, the Federal Circuit Court of Appeals has held that "[o]bviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching, suggestion or incentive supporting the combination." *In re Geiger*, 815 F.2d 686, 688 (Fed. Cir. 1987); also see *ACS Hospital Systems, Inc. v Montefiore Hospital,* 7322 F.2d

1572, 1577 (Fed. Cir. 1984). The only incentive provided by the Examiner is "at the time the invention was made, immunogenic particles appeared to be the best method of inducing protective immunity." This proposed incentive is conclusory and does not explain why one of ordinary skill would make the specific combination of references relied upon by the Examiner. Absent such a showing in the prior art supporting the combination, it is impermissible for the Examiner to search through the prior art for the claimed elements and combine them as claimed. *In re Vaeck,* 947 F.2d 488 (Fed. Cir 1991); I*n re Bond,* 910 F.2d 831 (Fed. Cir. 1990); and *In re Laskowski,* 871 F.2d 115 (Fed. Cir. 1989).

Therefore, Applicants respectfully request that the Examiner withdraw the rejections under 35 U.S.C. § 103.

Summary

Applicants submit that for the above-stated reasons the claims and specification comport with the requirements of 35 U.S.C. §102, 103, and 112 . Applicants respectfully request that the rejections be reconsidered and withdrawn, and a Notice of Allowance be issued.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, Applicant petitions for any required relief including extensions of time and authorizes the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this

document to **Deposit Account No. 03-1952**. The Assistant Commissioner is not, however, authorized to charge the cost of the issue fee to the Deposit Account.

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Respectfully submitted,

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